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**A novel humanized mouse model to track active and latent CNS HIV-1 infection and to test therapeutic interventions.**

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Human immunodeficiency virus type 1 (HIV-1) is a global health concern affecting more than 38 million people worldwide. It is an incurable disease attributed to the persistence of latent viral reservoirs that resume replication when antiretroviral therapy (ART) is stopped. Moreover, while ART can suppress viremia to undetectable levels, people with HIV-1 (PWH) experience increased premature aging and inflammation-associated pathophysiology than uninfected people. The central nervous system (CNS) carries a heavy disease burden with HIV-1-associated neurocognitive disorder (HAND) affecting 20-50% of PWH. Our recent studies in human postmortem brain showed that HIV-1 infection occurs predominantly in microglia and provirus integration are linked to inflammation-associated reprogramming of microglial transcriptomes and 3D genomes. Mechanisms governing HIV-1 latency in microglia are largely unknown due to difficulty distinguishing transcriptionally silent and latently infected cells. Here, we present a novel chimeric mouse model where human induced pluripotent stem cells (iPSC)-derived microglia are xenografted into mouse brains. Using iPSC that are genetically engineered to carry a Cre-recombinase activated fluorescent reporter switch enables us to permanently mark cells that have been infected with an Cre-expressing HIV-1 clone. This innovative molecular tool called HIV-1 induced lineage tracing (HILT) enables us to track infected cells and study the cell and proviral states underlying latency in the CNS at a single cell resolution. Our mouse model provides a quantitative tool to study new molecular and epigenetic strategies for reducing HIV-1 latent reservoir and to test the impact of therapeutic inflammation-targeting drug interventions on CNS HIV-1 reservoir. Supported by NIDA R01DA054526.